Advances in the Treatment of Urinary Tract Infection and Bacteriuria in Pregnancy

Allison Grant, MD*, Ketty Bai, BS, Gina M. Badalato, MD, Matthew P. Rutman, MD

KEYWORDS

• Asymptomatic bacteriuria • Urinary tract infection • Pregnancy • Pyelonephritis • Antibiotics in pregnancy

KEY POINTS

- In pregnant women, the prevalence of asymptomatic bacteriuria (ASB) is 2% to 10%, urinary tract infection (UTI) is 1% to 4%, and pyelonephritis is 1% to 4%, with *Escherichia coli* being responsible for a vast majority (49%–85%) of these UTIs.
- Midstream, clean-catch urine culture early in pregnancy is the gold standard for ASB screening, as well as the preferred test for UTI diagnosis (greater than 10^5 colony forming units/mL of urine).
- Maternal complications from ASB and UTI include pyelonephritis, preterm birth, and pre-eclampsia with some data challenging the notion that ASB specifically increases risk of preterm birth. Historically, maternal UTI and ASB in pregnancy were thought to put the fetus/newborn at a risk for intrauterine growth restriction and low birth weight. However, recent research has refuted this association.
- In general, the treatment course for cystitis and ASB is 5 to 7 days, whereas treatment for pyelonephritis warrants intravenous antibiotics and a 14 day course.

INTRODUCTION

Background

Urinary tract infection (UTI) is defined as a symptomatic infection of the urinary bladder and/or kidney, known as cystitis and pyelonephritis, respectively. Common symptoms include dysuria, urgency, frequency, suprapubic discomfort, and hematuria. Asymptomatic bacteriuria (ASB), on the other hand, refers to the presence of bacteria in urine without signs of infection or associated urinary symptoms.[1] UTIs in women usually occur due to an ascending infection of pathogenic bacteria naturally residing in the lower GI and genitourinary tract, most commonly *Escherichia coli* (*E. coli*).[2] Uncomplicated, or simple UTI, refers to cystitis in non-pregnant, afebrile, immunocompetent women with no anatomic or functional abnormalities of the genital tract. Complicated UTI refers to urinary infection of an individual with at least 1 factor that increases the risk of acquiring UTI, or decreases the efficacy of therapy, such as pregnancy, male gender, immunocompromised status, and anatomic or functional abnormalities of the genital tract.[3] As such, all UTIs in pregnancy are categorized as complicated.

During pregnancy, the urinary tract undergoes significant anatomic and physiologic changes as early as 7 weeks gestation, which may put these women at risk of developing ASB and/or UTI. Hormonal changes such as elevated progesterone lead to urothelial smooth muscle relaxation, resulting in decreased ureteral peristalsis and decreased bladder tone. The resulting ureteral dilation and increased bladder capacity may allow for urinary

Department of Urology, 161 Fort Washington Avenue, 11th floor, New York, NY 10032, USA
* Corresponding author.
E-mail address: ALG2247@cumc.columbia.edu

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stasis and create a pathway for bacteria to ascend the urinary tract.[1,4,5] Furthermore, as the gravid uterus grows, it displaces the bladder anterosuperiorly and can mechanically obstruct the ureter(s) at the pelvic brim. This dextrorotated uterus can also result in right-sided physiologic hydronephrosis of pregnancy.[6] Collectively, these anatomic and physiologic changes may increase the risk of UTI pathogenesis or urinary colonization.

During prenatal care, screening for ASB and monitoring for UTIs are important, as untreated infections can have adverse implications for maternal and fetal health. Both of these conditions have specifically been linked to maternal pyelonephritis/urosepsis, preterm labor, low birth weight, prematurity, and neonatal sepsis.[7,8] While fetal complications often arise as a consequence of maternal pyelonephritis/urosepsis, it is noteworthy that literature has documented these complications may exist even in the absence of such maternal conditions.[9,10] Herein, we provide an up-to-date review of the presentation and diagnosis, complications, and management of asymptomatic bacteriuria and UTIs in pregnancy.

Epidemiology of Urinary Tract Infections and Bacteriuria in Pregnancy

Prevalence and incidence

Due to the anatomic and physiologic changes in pregnancy that facilitate bacterial growth and colonization in the urinary tract, the incidence and prevalence of UTIs tend to increase in pregnancy. Prevalence of ASB in the general population is found to be the highest in women, with 1% to 6% prevalence in pre-menopausal non-pregnant women compared to 2% to 10% prevalence in pregnant women. More recently, a 2023 systematic review and meta-analysis reviewed 27 studies involving 30,641 pregnant women, determining the prevalence of symptomatic and ASB in this population to be 23.9%.[11] Furthermore, pregnant women are less likely to have spontaneous resolution of bacteriuria and are more likely to progress to UTI.[12] The prevalence of acute cystitis is reported in the literature to range from 1% to 4% in pregnant women.[13–17]

When ASB is untreated in pregnancy, 15% to 45% of patients go on to develop pyelonephritis. Pyelonephritis occurs in 1% to 4% of all pregnancies and is the most common non-obstetric cause of hospitalization during pregnancy in the United States (US). Conversely, in non-pregnant, healthy individuals, ASB can frequently spontaneously resolve without any associated long-term adverse outcomes.[18,19]

Risk factors during pregnancy

Risk factors that propagate urinary pathogenesis in the general population have been well-documented in the literature. These variables include childhood infections, dehydration, constipation, and voiding dysfunction.[20–22] While pregnant women have many of the same risk factors as their non-pregnant counterparts, the physiologic changes seen in pregnancy can put pregnant patients at greater risk.[20,23] This is supported by evidence that pyelonephritis is most common in the third trimester when the urinary tract changes are most significant,[24] with an estimated 50% to 90% of pregnant women demonstrating physiologic hydronephrosis by this time.[4]

Studies have also found certain demographic characteristics to be associated with increased risk of UTI in pregnancy. Historically, it was believed that lower socioeconomic status, multiparity, diabetes mellitus, and sickle cell trait were associated with an increased risk of UTI in pregnancy.[25] However, a 2006 study found no difference in rates of cystitis and ASB in pregnant women with sickle cell trait when compared to those without.[26] Furthermore, studies report inconsistent conclusions when evaluating the association of multiparity and low socioeconomic status with UTIs in pregnancy.[1,27] A recent retrospective study using the data from the National Birth Defects Prevention Study found the prevalence of UTIs was highest among women younger than 19 years of age at conception, those who self-reported American Indian or Alaska Native ethnicity, had low educational attainment, and those with an annual household income less than $10,000.[2]

Another risk factor for ASB or UTI in pregnancy is gestational diabetes mellitus. Notably, a 2023 meta-analysis[28] of 16 studies involving over 1.5 million pregnant women with gestational diabetes and their healthy counterparts investigated the association of gestational diabetes with infections during pregnancy. The study concluded that there was a significant association between gestational diabetes mellitus and the development of UTIs during pregnancy.

Microbiology of Urinary Tract Infection and Bacteriuria in Pregnancy

Common causative microorganisms

Unsurprisingly, the organisms responsible for UTI and bacteriuria in pregnancy are the same uropathogens that often colonize the urine and/or cause infections in non-pregnant women (**Table 1**). The most common causative pathogen is *E. coli*. Other gram-negative species such as *Klebsiella*,

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Table 1
Common causative microorganisms of urinary tract infection and bacteriuria in pregnancy

Type of Microbe	Microorganisms	Comments
Gram-negative	*Escherichia coli*	• Most common causative microorganism • Found in GI tract and fecal flora
	Klebsiella pneumoniae	• Increased risk of struvite kidney stones • Found in GI tract and fecal flora
	Proteus mirabilis	• Increased risk of struvite kidney stones
	Pseudomonas spp	• Increased risk of struvite kidney stones
Gram-positive	Group B *Streptococcus*	• Most common gram-positive causative microorganism • If untreated, may cause neonatal sepsis and obstetric complications (preterm labor, preterm delivery)
	Enterococcus spp	• Found in GI tract • Majority of infections due to *E. faecalis* and *E. faecium*
	Staphylococcus saprophyticus	• Common cause of uncomplicated UTIs in young, sexually active women • Found in normal genitourinary and GI tract flora
	Staphylococcus aureus	• Uncommon cause of UTI

Abbreviations: GI, gastrointestinal; UTI, urinary tract infection.

Proteus, and *Enterobacter* are also frequently isolated. Gram-positive species such as *Enterococcus*, *Staphylococcus*, and *Streptococcus* are less commonly identified in the urine.[1,16,29]

E. coli, a gram-negative organism originating in the GI tract and fecal flora, often colonizes the peri-urethral area. Herein, *E. coli* has ascending access into the genitourinary tract, making for a conducive environment for urinary colonization or infection. It is responsible for a vast majority of UTIs in pregnancy, ranging from 49% to 85%.[1,16,30–32]

Gram-positive organisms, most often group B *Streptococcus* (GBS), comprise roughly 10% of UTIs in pregnancy. Additional data reveal that substantial GBS titers are present in the urine of 7% of pregnant women.[1,33,34] GBS, like *E. coli*, is frequently detected in the GI flora. GBS may also be found in the reproductive tract of all females, serving as yet another source for GBS colonization. Moreover, a meta-analysis featured in *The Lancet Global Health* reported that, in the year 2020, an estimated 19.7 million pregnant women worldwide were identified as carriers of GBS.[33,35]

GBS identification in urine or rectovaginal flora peri-partum is critical, as GBS colonization can cause neonatal sepsis and is associated with several obstetric complications such as preterm rupture of membranes, preterm labor, and preterm delivery.[16] Neonatal GBS colonization or infection occurs when GBS is vertically transmitted from the mother to the baby as it passes through the vaginal canal during delivery, making screening for GBS colonization essential. The American College of Obstetricians and Gynecologists (ACOG) recommends GBS screening with a recto-vaginal swab between 36 weeks and 37 weeks 6 days gestation. Intrapartum antibiotic prophylaxis, most often penicillin or amoxicillin, unless an allergy is present, is given to reduce the risk of transmission to the baby at birth.[16,36] Antibiotic prophylaxis is indicated in mothers with GBS positive recto-vaginal swabs, GBS bacteriuria during the pregnancy, or history of neonate with invasive GBS disease. If a laboring patient has unknown GBS status, intrapartum prophylaxis is given in the presence of certain risk factors such as preterm labor, amniotic membrane rupture for more than 18 h, and intrapartum temperature greater than 100.4°F.[36]

Impact of nephrolithiasis on bacteriuria/urinary tract infection

Colonization or infection with urease-splitting bacteria such as *Klebsiella*, *Proteus*, *Pseudomonas*, or certain *Staphylococcus* species can cause urinary alkalization and struvite stone formation. Conversely, the presence of kidney stones in pregnancy has been associated with an increase in the risk of UTI and bacterial persistence and reinfection.[37,38] A systematic review and meta-analysis of 4.7 million pregnancies across North America, Europe, Asia, and Africa, determined the pooled incidence of renal stones in pregnancy to be

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0.49%. The analysis revealed a significant association between renal stones and the development of preeclampsia and UTIs (ASB, cystitis, and pyelonephritis).[37] Moreover, contemporary studies have reported that approximately 33% to 50% of pregnant women with stones will suffer from UTIs.[38,39]

Clinical Presentation and Diagnosis

Signs and symptoms of urinary tract infections in pregnant women

The signs and symptoms of UTI in pregnant women are similar to those in non-pregnant women. Whereas ASB, by definition, presents without symptoms, acute cystitis most often presents with symptoms such as suprapubic discomfort, dysuria, urgency, frequency, nocturia, and hematuria. It is important to note that these symptoms may result from physiologic changes in pregnancy and therefore must be accompanied by a positive urine culture to qualify as an UTI.[13] Patients with acute cystitis are afebrile, with no signs of systemic illness. Acute pyelonephritis, on the other hand, may present with systemic symptoms such as fever, nausea, vomiting, and chills, as well as flank pain. In acute pyelonephritis, the symptoms of acute cystitis may or may not be present.[16]

Screening and diagnosis of urinary tract infections in pregnancy

The routine screening of ASB in pregnancy is recommended by major guidelines from North America, South America, Australia, and most of Europe. The Infectious Diseases Society of America,[40] US Preventive Services Task Force (USPSTF),[18] and ACOG[13] currently recommend a midstream, clean-catch urine culture early in pregnancy as the gold standard for ASB screening. Notably, the USPSTF downgraded its recommendation from A to B level in 2019 due to increasing concerns of antimicrobial resistance, potential adverse effects of antibiotics on the microbiome, and lack of recent clinical trials studying the use of updated antibiotic regimens.[18]

A quantitative urine culture is the test used to diagnose UTI,[41] with a threshold of 10^5 colony forming units (CFU) per mL of urine. In studying urinalysis as a screening tool, nitrites have been found to be the most specific dipstick finding for UTIs in pregnant women. However, a recent study found that among its cohort of pregnant women with significant bacteriuria, none had positive nitrites. It hypothesized that nitrites may better indicate ongoing UTI rather than ASB.[42]

Other patient-specific variables may affect the accuracy of urinary diagnostic testing. A study of pregnant women found that increased body mass index provided a significantly increased risk of contaminated urine samples; this same study found that, on multivariable analysis, maternal age, gestational stage, and parity did not significantly increase risk of contamination.[43]

DISCUSSION

Complications and Risks

The significance of UTI and ASB during pregnancy lies in their potential to give rise to complications for both the mother and the fetus/newborn.

Maternal complications

UTIs, as well as ASB, put pregnant women at risk for pyelonephritis, pre-eclampsia, preterm labor, and septic shock.[1,5,16,30]

Pyelonephritis

Acute pyelonephritis, an ascending bacterial UTI causing inflammation of the kidneys, most often presents with fever, flank pain, costovertebral angle tenderness, and urinary symptoms, with or without associated nausea and vomiting. Similar to the general population, pregnant women with pyelonephritis are at risk of developing sepsis and acute kidney injury. However, pregnant women with pyelonephritis are at an additional increased risk of developing disseminated intravascular coagulation, anemia, acute respiratory distress syndrome, and preterm birth.[5,19,30,44]

The incidence of acute pyelonephritis in pregnancy varies by source and ranges from 0.5% to 4%.[19,30,44,45] Women are most affected in the second or third trimesters, with first trimester infection comprising only 10% to 20% of cases.[30,44] Data show that pregnant women with untreated first trimester ASB are more likely to develop pyelonephritis, relative to their ASB negative counterparts. Specifically, a prospective cohort study with an embedded randomized control trial found the incidence of pyelonephritis to be 2.4% in the ASB group and 0.6% in the ASB negative group.[46] These findings support treating ASB in pregnant women. Furthermore, a 2014 18-year retrospective cohort study reported an association between pyelonephritis in pregnancy with Black race and Hispanic ethnicity, young age, lower education level, nulliparous status, delayed access to prenatal care, and history of smoking during pregnancy.[30]

Preterm labor

In the past, untreated ASB had a known association with preterm labor, likely due to the predisposition to developing pyelonephritis.[1,5,16,30] However, contemporary studies raise skepticism

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on this association. After the introduction of screening for ASB, the USPSTF systematically reviewed outcomes in pregnant women. Of the 6 studies that reported on differences in preterm birth between those treated and untreated for ASB, 3 reported a decrease in preterm births with antibiotic treatment, while 3 studies reported no significant difference in delivery outcomes.[47] Furthermore, a 2015 prospective cohort study/randomized controlled trial[46] found there was no significant change in preterm delivery at less than 34 weeks between the ASB positive and ASB negative group.

Unsurprisingly, data support that UTIs, rather than ASB, in pregnancy increase the likelihood of preterm labor.[1,5,16,31] A retrospective cohort study published in 2021 evaluated the risk of preterm (<37 weeks) and early term (37 and 38 weeks) birth among women seen in a hospital for UTI. The researchers found that pregnant women with an UTI diagnosis had a 1.4 times greater risk of preterm delivery.[48]

Clearly, the current data continue to support the notion that symptomatic UTI in pregnancy increases risk of preterm labor, upholding the indication to treat pregnant women in this scenario. On the contrary, contemporary data question the previously established belief that ASB increases risk of preterm labor. The treatment of ASB in pregnancy, as it relates to preterm birth, remains an active area of research.

Preeclampsia

Pre-eclampsia is a condition characterized by proteinuria and hypertension (blood pressure >140/90 mm Hg) after 20 weeks gestation. The diagnosis carries high maternal and fetal or newborn morbidity and has historically been associated with UTI and ASB in pregnancy. Recent research has found that women with pre-eclampsia are 6.8 and 7.7 times more likely to have significant bacteriuria than those without pre-eclampsia.[49,50] Furthermore, a 2018 meta-analysis[51] utilizing 19 observational studies on UTI (defined as a positive urine culture regardless of symptoms) and pre-eclampsia upheld prior literature findings. The meta-analysis found UTI to be a risk factor for development of pre-eclampsia, with a pooled odds ratio of 1.31.

Fetal and neonatal complications

In terms of risks to the fetus, UTI and ASB have been associated with prematurity, low birth weight, and neonatal sepsis. As discussed earlier, UTI and ASB predispose the mother and fetus to preterm birth, and therefore, any complication that may result from prematurity.

Low birth weight

Historically, maternal UTI and ASB in pregnancy were thought to put the fetus/newborn at risk for intrauterine growth restriction and low birth weight,[16,47,52] an association that has been called into question in recent years. A 2019 study by USPSTF[47] did in fact identify a reduction in the incidence of low birth weight with the implementation of ASB screening (pooled relative risk 0.64; 95% confidence interval, 0.46–0.90), which upholds the existing belief. However, other contemporary studies report the conflicting data. Some report no significant difference in birth weight between neonates of mothers with UTI or ASB and neonates of mothers without UTI or ASB.[9,31]

Neonatal sepsis

Neonatal sepsis, while uncommon, is a feared complication of maternal UTI or ASB in pregnancy. As discussed in an earlier section, newborns of a GBS colonized mother are at increased risk of neonatal sepsis with an incidence of roughly 0.2%.[53] A 2023 prospective cohort study[32] collected urine cultures from 4506 pregnant and non-pregnant women and, among other things, evaluated what factors put neonates at an increased risk for sepsis. Within the group of pregnant women with UTI, *E. coli* and *Klebsiella* were the isolated microorganisms. The authors found that the presence of *E. coli* was significantly associated with neonatal sepsis after cesarean section (C-section) compared to the presence of *Klebsiella*.[32]

Prevention and Management

Antenatal screening for asymptomatic bacteriuria

While UTIs often present with symptoms, and thus, prompt evaluation with urine culture, ASB is identified by routine screening practices in the absence of symptoms. Per ACOG 2023 guidelines, current practices involve screening with a urine culture just once early on in the pregnancy, with the exact optimal time for culture being unknown.[13,54] Urine culture continues to be the gold standard screening method, as the data have shown other rapid urine screening tests in pregnancy to have poor performance metrics.[54]

Screening for ASB is a widely accepted practice in the US, but it is worthwhile to note that internationally there is still some discrepancy on the topic. An international review of 13 guidelines on management of UTI in pregnancy from 4 continents revealed that 85% (11/13) of the guidelines agreed with this standard. This leaves 2 of the 13 guidelines that do not recommend systematic screening for ASB in pregnancy.[55]

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Prevention

Efforts to prevent UTI and ASB in pregnancy are critical. Lowering the incidence of UTI will not only decrease maternal and fetal health risks associated with the uropathogens themselves, but also reduce the risk of antibiotic side effects and limit the contribution to antibiotic resistance.

Screening for ASB is a form of prevention of further development of symptomatic cystitis or pyelonephritis. While there is no robust research on behavioral modifications, such as pre/post coital voiding, front to back wiping, avoiding hot tubs/baths in prevention of UTI in pregnancy, a 2018 systematic review evaluated the utility of non-antibiotic preventive measures.[56] The paper identified 8 eligible articles and identified 5 safe non-antibiotic approaches to prevent UTI in pregnancy. The use of cranberry juice, hygienic measures, anti-bacterial immunization, Canephron (phytotherapeutic medicine comprised of 3 herbs), and ascorbic acid were reported to be safe and effective at preventing UTI in pregnancy, with hygiene behavior having the most reputable evidence. While the remaining 4 approaches did not have robust evidence with adequate power to recommend these practices in evidence-based guidelines, the initial findings suggest these practices may be protective against UTI in pregnancy and warrant further research.[56]

Treatment

Asymptomatic bacteriuria Once ASB is diagnosed, the patient should be treated with a 5 to 7 day course of culture-specific antibiotics. There is insufficient evidence to recommend for or against sending additional cultures following treatment to test for cure.[13]

The importance of treating ASB in pregnancy was highlighted in a Cochrane Library Systematic Review and Meta-Analysis published in 2019.[54] The authors synthesized data from 15 studies including over 2000 pregnant women with ASB to evaluate the effect of antibiotic treatment on the development of pyelonephritis, preterm birth, and low birth weight. The authors concluded that treatment with the antibiotics may be associated with reduction of incidence of preterm birth (3 studies), pyelonephritis (12 studies), low birth weight (6 studies), and persistent bacteriuria at delivery (4 studies). However, much of the evidence was of low certainty. Further, randomized studies have determined that a 5 to 7 day course of antibiotics is superior to a single dose in terms of cure rate and decreased incidence of low birth weight, but no difference in bacteriuria recurrence, pyelonephritis, or preterm birth.[13,57]

Urinary tract infection Similar to the treatment of ASB in pregnancy, UTI in pregnancy should be treated with a 5 to 7 day course of culture-specific antibiotic therapy. Repeat urine culture should only be sent if urinary symptoms recur 1 to 2 weeks following treatment. Clinicians may consider daily antimicrobial suppression throughout pregnancy for those patients with recurrent UTI. Furthermore, pregnant women with pyelonephritis should be treated in the inpatient setting with 14 days of intravenous antibiotics.[13]

While the 5 to 7 day course of antibiotics is widely accepted for the treatment of ASB and UTI, clinicians and researchers continue to investigate alternative treatment regimens in an effort to minimize antibiotic exposure and optimize treatment. In 2022 Schulz and colleagues[58] performed a systematic review and meta-analysis to compare single-dose antibiotic therapy with multi-dose therapy in lower UTIs in pregnancy. A total of 9 studies involving 1063 women were included. Antibiotics used in the single-dose regimens were fosfomycin, amoxicillin, ampicillin, and bactrim. Surprisingly, single-dose treatment, when compared to multiple day antibiotic regimens, had statistically similar results in clearing the urine culture of significant bacteria. This finding warrants further investigation, given that most guidelines recommend full multiple-day antibiotic regimens.

Antimicrobial therapy Antimicrobial safety profiles in pregnancy must be a foremost consideration when selecting a treatment regimen. Further, as with any other bacterial infection, the antibiotic choice is aimed at targeting the isolated pathogen.

Corrales and colleagues[55] nicely synthesized proposed antibiotic regimens for ASB, cystitis, and pyelonephritis in their 2022 review. They reported the first-line antibiotics: (1) for ASB to be nitrofurantoin, fosfomycin, and amoxicillin, (2) for cystitis to be nitrofurantoin, fosfomycin, trimethoprim, cephalexin, amoxicillin, and amoxicillin/clavulanate, and (3) for pyelonephritis to be ceftriaxone or cefuroxime $\pm$ gentamicin, ampicillin/gentamicin, or amoxicillin/gentamicin. These findings are similar to the antimicrobial recommendations put forth by ACOG 2023 guidelines.[13] ACOG; however, does not make a distinction between ASB and cystitis for antibiotic choice, recommending nitrofurantoin, cephalexin, trimethoprim-sulfamethoxazole, fosfomycin, amoxicillin, or amoxicillin-clavulanate. Pyelonephritis requires intravenous administration of antibiotics to improve tissue penetration. Recommended antibiotics are ampicillin/gentamicin, ceftriaxone, cefepime, and for those with a beta-lactam allergy, aztreonam.[13] The safety considerations of

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Table 2
Recommended and contraindicated antimicrobials for treatment of asymptomatic bacteriuria, acute cystitis, and pyelonephritis during pregnancy

Indication	Antimicrobial	Dosage	Duration	Considerations
Asymptomatic Bacteriuria/Acute Cystitis	Nitrofurantoin	100 mg PO q12 h	5–7 d	• Can be used in all trimesters; however, risk of facial malformation in first trimester and hemolytic anemia in the third trimester • Commonly used for lower UTIs ○ Achieves excellent therapeutic level in urine • Not used for pyelonephritis ○ Poor tissue penetration • Bactericidal activity against common uropathogens with limited resistance • No activity against *Proteus, Serratia, and Pseudomonas*
	Cephalexin	250–500 mg PO q6h	5–7 d	• First generation Cephalosporin • Good safety profile
	Sulfamethoxazole-trimethoprim	800/160 mg q12 h	5–7 d	• Not first-line in pregnancy • *Avoid in first trimester due to teratogenic risk of neural tube defects* ○ If no alternative treatment use with folic acid 5 mg/24h • If taken in third trimester, risk of neonatal hyperbilirubinemia and kernicterus
	Fosfomycin	3 g PO	Single dose	• Phosphonic acid derivative with broad coverage including MDR organisms; ESBL, MRSA, and VRE • Maintains high concentrations in urine for 3 d • Multiple randomized studies found no adverse outcomes with single-dose use
	Amoxicillin	500 mg PO q8h 875 mg PO q12 h	5–7 d	• First-line in pregnancy for sensitive bacteria • High rates of resistance in *E. coli* • Penicillins are oldest group of antibiotics with safety profile in pregnancy • Especially useful for treatment of *GBS*
	Amoxicillin–clavulanate	500 mg PO q8h 875 mg PO q12 h	5–7 d	• Risk of necrotizing enterocolitis in neonates • Suitable option throughout pregnancy

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Table 2
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Indication	Antimicrobial	Dosage	Duration	Considerations
Pyelonephritis	Ampicillin + gentamicin	2g IV q6h 1.5 mg/kg IV q8h 5 mg/kg IV q24 h	After clinical improvement, should be transitioned to appropriate oral antimicrobial based on culture sensitivities to complete 14-d course of antimicrobial therapy	• Theoretic risk of ototoxicity and nephrotoxicity in mother and fetus, although have not been documented in literature • Gentamicin is the preferred aminoglycoside in pregnancy due to higher safety profile
	Ceftriaxone	1g IV q24 h		• Third generation Cephalosporin with good gram-negative and gram-positive coverage • Can be used in mild penicillin allergy • Well-established safety profile in pregnancy • If patient unstable, consider adding Gentamicin
	Cefuroxime	500 mg q12 h		• Second generation Cephalosporin • See Ceftriaxone
	Cefepime	1g IV q12 h		• Fourth generation Cephalosporin • See Ceftriaxone
	Aztreonam	1g IV q8-12h		• Low cross reactivity with Penicillin allergy • No harmful effects on fetus seen in animal studies although well-designed studies in pregnant women are lacking
Contraindications	Streptomycin	N/a	N/a	• Aminoglycoside drug class • Irreversible bilateral deafness • FDA pregnancy category rating D
	Tetracycline Minocycline Doxycycline			• Tetracycline drug class • Contraindicated past the 5th week of gestation • Permanent tooth discoloration, bone anomalies • FDA pregnancy category rating D
	Ciprofloxacin Levofloxacin			• Fluoroquinolone drug class • Renal toxicity, cardiac defects, central nervous system toxicity in fetus • May be safe in first trimester, but generally not recommended • FDA pregnancy category rating C

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Tigecycline	• Glycylcycline drug class • Fetal loss in animal studies, no human studies performed • FDA pregnancy category rating D
Sulfamethoxazole-trimethoprim	See ASB/Acute cystitis section
Nitrofurantoin	See ASB/Acute cystitis section

FDA Pregnancy Category Rating C: risk not ruled out. Animal studies show negative impacts on fetus, but no robust human studies. FDA Pregnancy Category Rating D: evidence of risk to human fetuses established through human studies.

Abbreviations: ASB, asymptomatic bacteriuria; ESBL, extended-spectrum beta-lactamases; FDA, Food and Drug Administration; GBS, group B *Streptococcus*; MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococci*.

Data from Refs.[1,13,55,60]

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these antimicrobials, including the trimesters in which certain antibiotics should be avoided, are outlined in Table 2.

It is important to note that the recommended dose and schedule of fosfomycin are 3 g orally 1 time. Fosfomycin has been proven to have equivalent clinical outcomes relative to multi-day antibiotic counterparts. As such, the use of fosfomycin is seen as an exception to the concept that multi day antibiotic regimens prevail over single-dose therapy.[13,59]

Careful antibiotic choice is critical when treating pregnant women for ASB or UTI, as certain antibiotics in pregnancy carry irreversible and devastating risks to the fetus. While some antimicrobials, such as streptomycin and the tetracyclines, are contraindicated throughout the entire pregnancy, other antibiotics, such as nitrofurantoin and sulfamethoxazole-trimethoprim are safe only during certain trimesters, and carry significant risk in other parts of the pregnancy.[60] A summary of recommended antibiotics and regimens, contraindicated antibiotics, and notable considerations, can be found in Table 2.

Antibiotic resistance patterns As with any bacteria, uropathogens in pregnancy are susceptible to developing resistance to antibiotics. For years there has been an increase in the prevalence of drug-resistant and multi-drug-resistant organisms.[1] A recent study revealed 92% of uropathogens to be resistant to at least 1 antibiotic, with the majority (80%) being resistant to 2 or more drugs.[61] Further literature has determined that the antibiotics with most uropathogen resistance are ampicillin, 2nd and 3rd generation cephalosporins, and trimethoprim-sulfamethoxazole, with *Proteus* and *Klebsiella* species having significant resistance to ciprofloxacin. Nitrofurantoin, carbapenems, and amikacin were the antibiotics with lowest rates of uropathogen resistance.[62,63] Interestingly, a 2023 prospective cohort study[32] collected urine cultures from 4506 pregnant and non-pregnant women and found that overall the uropathogens isolated from non-pregnant women had significantly more antibiotic resistance compared to the organisms isolated from pregnant women. The rising prevalence of antibiotic resistance, as well as the continued evolution of resistant patterns, highlights the importance of treating infections or ASB in pregnancy with culture-specific antibiotics, rather than empiric treatment.

FUTURE DIRECTIONS AND RESEARCH

Although there are well-established guidelines for screening and management of UTI and ASB in pregnancy, researchers and clinicians should not be dissuaded from engaging in research to further optimize urinary care for pregnant women. With constantly evolving microorganisms and antibiotic resistance patterns, research and antimicrobial stewardship are critical to improve our treatment regimens while protecting maternal and fetal health. Future research can focus on investigating novel prevention techniques and non-antibiotic management as seen in the Gouri and colleagues' study.[56] Additionally, an area that can be further explored is health care disparities and access to care amongst pregnant women, to better identify differences in, and barriers to, care that may contribute to worse outcomes in certain populations.

SUMMARY

UTIs in pregnancy can have significant adverse implications on maternal and fetal health. Physiologic changes during pregnancy, including hydroureteronephrosis and decreased bladder tone, cause an increased risk of UTI and ASB in pregnant women. The most common causative uropathogens in pregnant women are the same as those in their non-pregnant counterparts; however, pregnant women have GBS UTIs more commonly than non-pregnant women. All pregnant women should undergo an early pregnancy mid-stream urine culture screening test for ASB and diagnostic urine culture when presenting with urinary symptoms. A positive urine culture, regardless of symptoms, should be treated with appropriate antimicrobial therapy, as recommended by evidence based, published guidelines. Active and future research on non-antibiotic preventive measures, as well as on regimens to minimize antibiotic exposure for mother and fetus, continue to improve how we approach treating ASB and UTI in pregnancy, ultimately improving care for our patients.

CLINICS CARE POINTS

- In pregnant women, the prevalence of ASB is 2% to 10%, UTI is 1% to 4%, and pyelonephritis is 1% to 4%.[12,18]
- Prevalence of UTIs is highest among women less than 19 yearsof age at conception, self-reported American Indian or Alaska Native ethnicity, low educational attainment, and having an annual household income less than $10,000, in one study.[2]
- *E. coli* is responsible for a vast majority of UTIs in pregnancy ranging from 49% to 85%.[1,16,30–32]

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- GBS, frequently detected in the female GI and reproductive tract, is the most commonly found gram-positive organism, comprising roughly 10% of UTIs in pregnancy. Substantial GBS titers are present in the urine of 7% of pregnant women.[1,33]
- Midstream, clean-catch urine culture early in pregnancy is the gold standard for ASB screening, as well as the preferred test for UTI diagnosis (greater than 10^5 CFU/mL of urine).[13]
- Maternal complications from ASB and UTI include pyelonephritis, preterm birth, and pre-eclampsia with some data challenging the notion that ASB specifically increases risk of preterm birth.
- Historically, maternal UTI and ASB in pregnancy were thought to put the fetus/newborn at a risk for intrauterine growth restriction and low birth weight.[16,47,52] However, recent research has refuted this association.[9,31]
- The presence of *E coli* was significantly associated with neonatal sepsis after C-section compared to *Klebsiella*.[32]
- The use of cranberry juice, hygienic measures, immunization, Canephron, and ascorbic acid were reported to be safe and effective at preventing UTI in pregnancy, with hygiene behavior having the most evidence.[56]
- In general, the treatment course for cystitis and ASB is 5 to 7 days and for pyelonephritis treatment course should be 14 days.
- Understanding the mechanism of action and side effect profiles of antibiotic agents is paramount to optimize responsible and safe prescribing patterns during pregnancy.

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